Express Mail Label No.

UTILITY PATENT APPLICATION TRANSMITTAL
(Small Entity)

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No.
AML/10857.236

Total Pages in this Submission

TO THE ASSISTANT COMMISSIONER FOR PATENTS
Box Patent Application
Washington, D.C. 20231

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 C.F.R. 1.53(b) is a new utility patent application for an invention entitled:

CHITOSAN-XANTHAN BASED POLYIONIC HYDROGELS FOR STABILISATION AND CONTROLLED RELEASE OF VITAMINS.

and invented by:

Esteban Chornet
Severian Dumitriu

If a CONTINUATION APPLICATION, *check appropriate box and supply the requisite information:*

☐ **Continuation** ☐ **Divisional** ☐ **Continuation-in-part (CIP)** of prior application No.: _____

Which is a:

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Enclosed are:

Application Elements

1. ☒ Filing fee as calculated and transmitted as described below

2. ☒ Specification having 17 pages and including the following:

   a. ☒ Descriptive Title of the Invention
   b. ☐ Cross References to Related Applications *(if applicable)*
   c. ☐ Statement Regarding Federally-sponsored Research/Development *(if applicable)*
   d. ☐ Reference to Microfiche Appendix *(if applicable)*
   e. ☒ Background of the Invention
   f. ☒ Brief Summary of the Invention
   g. ☒ Brief Description of the Drawings *(if drawings filed)*
   h. ☒ Detailed Description
   i. ☒ Claim(s) as Classified Below
   j. ☒ Abstract of the Disclosure

UTILITY PATENT APPLICATION TRANSMITTAL
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Application Elements (Continued)

3. ☒ Drawing(s) *(when necessary as prescribed by 35 USC 113)*

   a. ☐ Formal b. ☒ Informal Number of Sheets 7

4. ☒ Oath or Declaration

   a. ☒ Newly executed *(original or copy)* ☐ Unexecuted

   b. ☐ Copy from a prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*

   c. ☒ With Power of Attorney ☐ Without Power of Attorney

   d. ☐ *DELETION OF INVENTOR(S)*
   Signed statement attached deleting inventor(s) named in the prior application, see 37 C.F.R. 1.63(d)(2) and 1.33(b).

5. ☐ Incorporation By Reference *(usable if Box 4b is checked)*
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

6. ☐ Computer Program in Microfiche

7. ☐ Genetic Sequence Submission *(if applicable, all must be included)*

   a. ☐ Paper Copy

   b. ☐ Computer Readable Copy

   c. ☐ Statement Verifying Identical Paper and Computer Readable Copy

Accompanying Application Parts

8. ☒ Assignment Papers *(cover sheet & documents)*

9. ☐ 37 CFR 3.73(b) Statement *(when there is an assignee)*

10. ☐ English Translation Document *(if applicable)*

11. ☒ Information Disclosure Statement/PTO-1449 ☒ Copies of IDS Citations

12. ☐ Preliminary Amendment

13. ☐ Acknowledgment postcard

14. ☐ Certificate of Mailing

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Docket No. AML/10857.236
Total Pages in this Submission

Accompanying Application Parts (Continued)

15. ☐ Certified Copy of Priority Document(s) *(if foreign priority is claimed)*

16. ☒ Small Entity Statement(s) - Specify Number of Statements Submitted: 1

17. ☐ Additional Enclosures *(please identify below):*

Fee Calculation and Transmittal

CLAIMS AS FILED

For	#Filed	#Allowed	#Extra		Rate	Fee
Total Claims	16	- 20 =	0	x	$9.00	$0.00
Indep. Claims	1	- 3 =	0	x	$39.00	$0.00
Multiple Dependent Claims (check if applicable) ☐						$0.00
					BASIC FEE	$380.00
OTHER FEE *(specify purpose)* Assignment						$40.00
					TOTAL FILING FEE	$420.00

☒ A check in the amount of **$420.00** to cover the filing fee is enclosed.

☒ The Commissioner is hereby authorized to charge and credit Deposit Account No. **07-1742** as described below. A duplicate copy of this sheet is enclosed.

- ☐ Charge the amount of as filing fee.
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- ☐ Charge the issue fee set in 37 C.F.R. 1.18 at the mailing of the Notice of Allowance, pursuant to 37 C.F.R. 1.311(b).

Dated:

Signature

Alain M. Leclerc **37036**

cc:

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) AND 1.27 (d)) - NONPROFIT ORGANIZATION

Docket No. AML/10857.236

Serial No.	Filing Date	Patent No.	Issue Date

Applicant/ Patentee: **CHORNET, Esteban**
DUMITRIU, Severian

Invention:

Chitosan-xanthan based polyionic hydrogels for stabilisation and controlled release of vitamins.

I hereby declare that I am an official empowered to act on behalf of the nonprofit organization identified below:

NAME OF ORGANIZATION: **UNIVERSITY OF SHERBROOKE**

ADDRESS OF ORGANIZATION: **2500 boul. de l'Université**
Sherbrooke, Québec,
Canada J1K 2R1

TYPE OF NONPROFIT ORGANIZATION:

- ☒ University or other Institute of Higher Education
- ☐ Tax Exempt under Internal Revenue Service Code (26 U.S.C. 501(a) and 501(c)(3))
- ☐ Nonprofit Scientific or Educational under Statute of State of The United States of America
  Name of State: Citation of Statute:
- ☐ Would Qualify as Tax Exempt under Internal Revenue Service Code (26 U.S.C. 501(a) and 501(c)(3)) if Located in The United States of America
- ☐ Would Qualify as Nonprofit Scientific or Educational under Statute of State of The United States of America if Located in The United States of America
  Name of State: Citation of Statute:

I hereby declare that the above-identified nonprofit organization qualifies as a nonprofit organization as defined in 37 C.F.R. 1.9(e) for purposes of paying reduced fees to the United States Patent and Trademark Office regarding the invention described in:

- ☒ the specification to be filed herewith.
- ☐ the application identified above.
- ☐ the patent identified above.

I hereby declare that rights under contract or law have been conveyed to and remain with the nonprofit organization with regard to the above identified invention.

If the rights held by the above-identified nonprofit organization are not exclusive, each individual, concern or organization having rights to the invention is listed on the next page and no rights to the invention are held by any person, other than the inventor, who could not qualify as an independent inventor under 37 CFR 1.9(c) or by any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

Each person, concern or organization to which I have assigned, granted, conveyed, or licensed or am under an obligation under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

☒ no such person, concern or organization exists.
☐ each such person, concern or organization is listed below.

FULL NAME _____
ADDRESS _____

☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization

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ADDRESS _____

☐ Individual ☐ Small Business Concern ☐ Nonprofit Organization

FULL NAME _____
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ADDRESS _____

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Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING: Michèle Desrochers

TITLE IN ORGANIZATION: Interim Director

ADDRESS OF PERSON SIGNING: 585, Victoria
Sherbrooke, Québec
Canada J1H 3J4

SIGNATURE: _____ DATE: Oct 28, 1998

ABSTRACT OF THE DISCLOSURE

A thermo- and photo stable composition comprising a chitosan/xanthan hydrogel including at least one thermo- or photo-sensitive substance chosen among the following: vitamins, amino-acids, nucleic acids, and polypeptides. The hydrogel can be adapted to release the thermo- or photo–sensible substances in either a human or an animal. The present invention also discloses a method of making these hydrogel composition. Additionally, the present invention presents a method of using these hydrogel composition in dermatology or as a food supplement.

TITLE OF THE INVENTION

Chitosan-xanthan based polyionic hydrogels for stabilisation and controlled release of vitamins

FIELD OF THE INVENTION

The present invention relates to chitosan/xanthan based hydrogels. More specifically, the present invention deals with chitosan/xanthan based hydrogels used in dermatology and as food additives, where such hydrogels are used as carrier for active compounds such as vitamins, amino-acids, nucleic acids, polypeptides, etc.

BACKGROUND OF THE INVENTION

The production of chitosan/xanthan hydrogels is known. US patents 5,620,706 and 5,648,252 describe such hydrogels as inert supports for enzyme immobilisation or for the controlled release of specific antibiotics or anticancer agents. However, the application of such hydrogels as supports, stabilisation and subsequent controlled release of vitamins, amino-acids, nucleic acids and polypeptides has not been proposed yet.

One of the key aspects in the preparation of food additives and dermatological preparations is the preservation of active ingredients prone to degradation, such as vitamins, amino-acids, nucleic acids and polypeptides. Exposure of such ingredients to heat or light accelerates their degradation.

Given the importance of the active ingredients mentioned above, several excipients, such as tablets, capsules, gellules, gels, lotions, ointments, emulsions and simple solutions, have been developed with a view to protect the active ingredients against degradation or simply to render them

hydrophobic. However, several drawbacks of these synthetic devices have been identified. In particular their irritation potential and toxicity were put forward.

Due to the inherent limitations of conventional excipients, the use of synthetic polycations was recently proposed. As an example, European patent application # 504 066 A1, 1992, to L'Oréal (France) proposes cosmetic compositions comprising a dispersion of active solid particles coated with a cationic polymer. The aim of the polymeric coating being to increase the stability of the overall composition in addition to preventing degradation of the active ingredient.

Yet an important objective remains unfulfilled. Indeed, there remains an important need to develop new excipients capable of being used in food and dermatological preparations to stabilise thermo- or photo sensitive active ingredients, such as vitamins, nucleic acids, amino-acids and polypeptides.

OBJECTS OF THE INVENTION

An object of the present invention is therefore to provide a hydrogel preparation for use as a delivery device for food or dermatological preparations with a concurrent objects of providing stabilization of thermo- and photo sensitive active ingredients and avoiding any irritation or toxicity potentials. A further object of the present invention is to disclose a method of dispersion of the active ingredient within the hydrogel matrix.

SUMMARY OF THE INVENTION

Generally, in accordance with the present invention, there is provided a preparation which stabilises thermo- and photo sensitive bioactive molecules. The preparation comprises a hydrogel made of a complex of

chitosan and xanthan. Within the hydrogel there is lodged at least one thermo- or photo sensitive substance chosen among the following: vitamins, amino-acids, nucleic acids and polypeptides. The hydrogel configuration and structure is prepared so as to release, in a controlled way, the thermo- or photo sensitive ingredients either in a human or animal subjects.

The present invention also discloses a method of making these hydrogels. The present invention also teaches the use of these hydrogels in dermatology or as a food additive vehicle.

Other objects, advantages and features of the present invention will become more apparent upon reading of the following non restrictive description of preferred embodiments thereof, given by way of example only with reference to the accompanying drawings.

Those specialised in the area covered by this invention will certainly be able to apply modifications or adaptations to the details described in the preferred embodiment while being constrained within the framework of the current invention.

BRIEF DESCRIPTION OF THE DRAWINGS

In the appended drawings:

Figure 1 is a complex of chitosan and xanthan;

Figure 2 is a diagram of the lab apparatus for kinetic studies;

Figure 3 is an amount of Vitamin C released as a function of time/ Sample coded VS2L. The hydrogel CHITOXAN™ – Vitamin C is prepared with CHITOXAN™ having a swelling index (α) of 1800%;

Figure 4 is the rate of release of Vitamin C as a function of time. Sample coded VS2L;

Figure 5 is the amount of Vitamin C released as a function of time/ Sample coded VS2R. The hydrogel CHITOXAN™ – Vitamin C is prepared with CHITOXAN™ having a swelling index (α) of 2200%;

Figure 6 is the rate of release of Vitamin C as a function of time. Sample coded VS2R ; and

Figure 7 is the variation of the % of Vitamin C released as a function of time. Sample coded VS2M. The hydrogel CHITOXAN™ – Vitamin C is prepared with CHITOXAN™ having a swelling index (α) of 3500%.

DESCRIPTION OF THE PREFERRED EMBODIMENT

The detailed description reveals compositions for food and dermatological applications comprising one or several active ingredients that are either prone to thermo- or photo degradation. These compositions are based on a polyionic hydrogels obtained by a chitosan/ xanthan complexing which incorporates therein the active ingredients thereby protecting them from thermo- or photo induced degradation while controlling their release thus enhancing their activity and the duration of this activity.

Also described are two methods of incorporation of the active ingredients in the hydrogel depending on the nature of the active ingredients. In a first method, liposoluble active ingredients are introduced in the hydrogel during the making of the hydrogel. In a second method, hydrosoluble active ingredients are introduced by diffusion in the already made hydrogel. Both methods can be used in sequence.

The present invention thus reveals a novel and surprising way of introducing various vitamins and other ingredients such as amino-acids, nucleic acids and polypeptides in hydrogels and of controlling the release of those ingredients in various drug delivery vehicles such as: capsules or gelcaps for oral ingestion, rectal suppositories, creams and ointments, gels, solutions and cutaneous patches.

The present invention further reveals a method of introducing in the same hydrogel liposoluble and hydrosoluble active ingredients.

Finally, the present invention further discloses methods of making food additives and dermatological creams incorporating the hydrogel.

It is to be noted that the terms "dermatologic" and "dermatological" are used in their widest sense thus covering both the dermatological and cosmetic applications. Furthermore, these terms are meant to cover direct skin treatments or treatment through nails or hair.

The term "food additive" is also to be understood in its widest sense including thus all food preparations where the additive has a nutritional or therapeutic function as well as simple mechanical functions such as that of a texturizing agent, filler or viscosity control agent.

The preparations covered by the present invention focus mainly on humans although they may be used in the veterinary field.

On figure 1, it is shown how the hydrogel of the present invention is an ionic complex between chitosan, a cationic natural polymer, and xanthan, an anionic natural polymer. A method of making of the hydrogel has been

described in US patent 5,720,206 granted to the same assignee as in the present application and is incorporated herein by reference. As shown in Figure 1, xanthan and chitosan form a complex, i.e. a network of ionic linkages between these two polymer molecules. The complex is a highly hydrophilic hydrogel.

(a) Inclusion of liposoluble vitamins in the chitosan-xanthan hydrogel

Vitamin A, also called Retinol, is a molecule extremely sensitive to light and oxygen. As a consequence, this vitamin may not be used in a cream unless it is being stabilised to counteract the negative effects of light and oxygen (from ambient air). The method of the present invention consists in stabilising Vitamin A in a hydrogel made of xanthan and chitosan complex. The xanthan and chitosan complex being described in US patent 5,620,706.

Example 1: Inclusion of Vitamin A when making the hydrogel

A solution (100 ml) of Vitamin A (10-20 w/v%) in ethanol is first prepared. This solution is added, under intense agitation, to 500 ml of a xanthan solution, 0.65w/v%. The final solution has a Vitamin A concentration between 1.66 and 3.33 w/v% . The solution is kept at 3°C. It is subsequently sprayed, via a nozzle, into 800 ml of a 0.65w/v% chitosan solution. The complexation reaction is conducted during 30 minutes. The gel formed is then filtered and rinsed with water to a pH of 6.8. In order to increase the hydrogel stability, a final washing with a sodium bicarbonate solution, 1 w/v%, brings the gel to a pH of 7.5. The gel is then frozen and freeze-dried. All these operations, including the freeze drying, are best conducted in the absence of light and oxygen.

Example 2: Inclusion of Vitamin A by diffusion

Using a previously prepared xanthan-chitosan hydrogel with a swelling index (α) of at least 2000%, it is possible to introduce the Vitamin A by diffusion. The swelling index (α) is defined as follows:

$$\alpha = 100\% \times \frac{\text{mass of swelled hydrogel in equilibrium - mass of dried hydrogel}}{\text{mass of dried hydrogel}}$$

Under these conditions, the time for the experiment is decreased thereby preventing the molecule's degradation. The method involves dissolving 0.07 g of Vitamin A in 1 ml of ethanol (96%) and adding 1.5 g of the freeze dried xanthan-chitosan complex having α = 2500%. Slight agitation allows the obtention of a homogeneous paste. 2 ml of ethanol, and 200 μl of water are then added under slight agitation and the mixture is kept at 4°C for 24 hours in absence of light. The alcohol is then evaporated, at 4°C. The final product can be freeze dried and has 46 mg of Vitamin A per g of freeze dried xanthan-chitosan complex.

Example 3: Inclusion of Vitamin E

The method (a) developed for Vitamin A is also applied for the inclusion of Vitamin E. The concentration of Vitamin E in the freeze dried hydrogel can reach 20 wt% .

Example 4: Inclusion of Vitamin K

The method (a) developed for Vitamin A is also applied for the inclusion of Vitamin K. The concentration of Vitamin K in the freeze dried hydrogel can reach 20 wt% .

(b) Inclusion of hydrosoluble vitamins in the chitosan-xanthan hydrogel

For bioactive hydrosoluble ingredients, it is preferable to use the diffusion method in the freeze dried hydrogel to avoid loss of ingredients that would

otherwise occur during the reaction between xanthan and chitosan. In this method, the xanthan-chitosan hydrogel must have a swelling index of at least 2000%.

Example 5: Inclusion of Vitamin C

Given the redox character of Vitamin C with regards to chitosan, a new method of inclusion has been developed. This method involves 2 steps:

Step 1: Preparation of the xanthan-chitosan complex (CHITOXAN™), i.e. the polyonic hydrogel;

Step 2: Incorporation of Vitamin C.

Step 1- Preparation of the xanthan-chitosan complex

Step 1 follows the method described in US Patent 5,620,706. Chitosan used has typically a molecular weight comprised between 250,000 and 350,000 and the hydrogel produced a swelling index of $\alpha \geq 2000\%$. The CHITOXAN™ thus produced is milled to obtain a fine powder of particles comprised between 250 and 500 μm.

Step 2 - Incorporation of Vitamin C

This step can be carried out via two different approaches:

2a. Stabilisation with amino-acids

To 10 ml of water are added 1 g of Vitamin C, 0.06 g of L-cysteine, 0.02 g of L-cystine and 0.02 g of L-methionine. To this solution, 1 g of freeze-dried CHITOXAN™ made of particles having diameters comprised between 250 and 500 μm is added. It is not necessary that the mixture have any excess liquid. Pure water may be added to complete the hydration for a period of 2 hours. All the operations preferably require the absence of light. The

mixture is then frozen, freeze-dried and milled to provide a final product made of particles having diameters comprised between 50 and 125 μm.

The Vitamin C thus incorporated in the freeze-dried hydrogel and hydrated shows a good stability, without coloration after 2 weeks at 45°C (wet hydrogel) and after 20 weeks at 45°C (dried hydrogel). It is also possible to use as "stabilisers" either tartaric acid at 0.1 wt%, metaphosphoric acid at 0.03 wt% or citric acid at 0.1 wt%. The percentage is expressed with respect to CHITOXAN™.

2b. Stabilisation with tripeptides

The previous method (2a) is used replacing the three amino-acids with a tripeptide having sulfur-containing functionalities. To 10 ml of water, g of Vitamin C and 0.002 g of glutathione are added. After 5 minutes of agitation, 1 g of CHITOXAN™ is added. The mixture is kept in slight agitation until a homogeneous paste is obtained. The mixture is left to stand for 2 hours to reach the equilibrium hydration. The paste is then frozen and freeze-dried. All operations preferably require absence of light.

(c) Extraction and determination of Vitamin C included in CHITOXAN™

Extraction

The solvent used is an aqueous mixture of 3% (w/v) metaphosphoric acid and 8% (v/v) acetic acid.

The method consists of introducing 20 to 30 mg of freeze-dried CHITOXAN™ loaded with Vitamin C in a 50 ml centrifuge tube together with 40 ml of the extraction solvent. The mixture is magnetically stirred for 60 minutes. The suspension formed is centrifuged (4000 rpm) and the supernatant is analysed. All operations are done in absence of light.

Analytical determination of Vitamin C

This determination requires the establishment of a calibration curve at a maximum absorption wavelength using a UV-vis spectrophotometer. A standard is prepared with the same solution (and solvent) initially used to introduce the Vitamin C within the CHITOXAN™. Experimentation has shown an absorption maximum at 243 nm for Vitamin C at 98% purity obtained from ALDRICH.

The calibration curve is constructed at 243 nm as follows. A solution of 1.3 mg/ml of Vitamin C in the solvent is prepared in a graduated cylinder. The solution is prepared just before analysis. By successive dilutions, the absorption versus concentration calibration curve (mg/ml) is thus measured.

The concentration of Vitamin C in the supernatant obtained via extraction is determined at 243 nm using the calibration curve. The concentration of Vitamin C in the sample prepared by method 2a is 49.6%.

(d) Inclusion of the CHITOSAN™ – Vit. C preparation in a cream

1 g of CHITOXAN™ – Vit. C preparation is hydrated with water until a creamy paste is obtained. Weighing the paste permits to calculate the amount of Vitamin C present. Subsequently, the paste is mixed, under strong agitation, with a base cream in order to achieve a final concentration in Vitamin C preferably comprised between 5 and 25 wt%.

(e) Determination of the Vitamin C stability in the cream base

10 g of the preparation obtained by inclusion of CHITOXAN™ – Vit. C in a cream base is introduced in a glass tube protected from exposure to light. The tube is heated at 45°C. In order to determine the rate of degradation of Vitamin C in the base cream, an aliquot is taken corresponding to a total

amount of 10 to 30 mg of Vitamin C. Such an aliquot is taken every day for the first four (4) days and, subsequently, every other day for a total of 30 days. Samples not immediately analysed were kept frozen at –4°C.

The aliquots were analysed with the method described earlier (always using the extraction solvent).

With samples VS2L, VS2R and VS2M, were prepared creams having concentrations of Vitamin C comprised between 5 and 25 wt%. Using the method previously described, Vitamin C inserted in CHITOXAN™ was found to be stable with no coloration of the cream appearing after 30 days at 45°C and the degradation of the Vitamin C was as little as 15 %. With a cream prepared with free Vitamin C (i.e. no hydrogel), an orange coloration appeared and a 98% degradation of Vitamin C occurred under the same conditions.

(f) Controlled release kinetics

Table 1 shows the types of CHITOXAN™ – Vit. C combinations studied. As illustrated in Figure 2, the controlled release kinetics is determined by introducing a precise quantity of the CHITOSAN™ – Vit. C preparation in the reactor.

Table 1: Types of CHITOXAN™ – Vit. C preparations studied

Preparations Codes CHITOXAN™ – Vit. C	Swelling index (α) of CHITOXAN™ %	Concentration of Vit. C in the CHITOXAN™ – Vit. C (wt%)
VS2L	1800	50.3
VS2R	2200	49.6
VS2M	3500	51.0

The solvent, a mixture of 3% w/v methaphosphoric acid and 8% w/v acetic acid, flows into the central tube directly into the reactor where it comes into contact with the CHITOXAN™ – Vit. C preparation. The Vitamin C is gradually released from the preparation and solubilizes inside the solvent. The latter leaves the reactor through small orifices ensuring constant circulation of the solvent and good contact with the preparation.

Figure 3 shows that the Vitamin C released from sample VS2L follows a linear increase as a function of time with two distinct slopes, depicted in Figure 4.

Figure 4 shows that with sample VS2L, the Vitamin C diffuses at a constant speed of 0.36 mg/min during the first period while it decreases by half for the 100 following minutes.

Sample VS2R also shows in Figure 5 the two distinct linear increase profiles with two distinct slopes depicted in Figure 6. The first slope is faster than that of preparation VS2L indicating a more rapid liberation. The second slope, at 0.02 mg/min, releases Vitamin C at a controlled but slow rate.

Figure 7 shows the liberation of Vitamin C for preparation VS2M. The release of 85% of the Vitamin C is achieved in the first 10 min.

The differences between the liberation profiles of the preparations are related to the swelling index. Sample VS2M, with a swelling index of 3500%, displayed a faster diffusion rate of Vitamin C than sample VS2R , α = 2200%, and the latter more rapid in turn than that of sample VS2L, α = 1800%. Thus the swelling index plays a key structural role in the release kinetics.

(g) Inclusion of CHITOXAN™ – Vit. C in a food mixture

Hydrogel CHITOXAN™ – Vit. C as well as other chitosan-xanthan hydrogels containing vitamins, nucleic acids, amino-acids and polypeptides can be used in hydrated food mixtures such as gels, sauces, syrups, etc. as well as in dehydrated mixtures.

The physical characteristics of the chitosan-xanthan hydrogel will determine the structure and more or less viscous texture of the final products. The choice of a hydrogel as described in the present invention will permit to adapt the hydrogel to diversified food applications.

Furthermore, the present invention also covers the production of tablets using CHITOXAN™ – Vit. C powder and other active ingredients as well when required. Thus, tablets made of freeze-dried powder of other chitosan-xanthan hydrogels containing different vitamins, amino-acids, nucleic acids and polypeptides and their combinations can be prepared.

Although the present invention has been described hereinabove by way of preferred embodiments thereof, it can be modified, without departing from the spirit and nature of the subject invention as defined in the appended claims. It is obvious that the present application can accommodate numerous other variations within the framework of the invention as described.

WHAT IS CLAIMED IS:

1. Thermo- and photo stable preparations comprising a chitosan-xanthan hydrogel, said hydrogel including in its matrix at least one thermo- or photo sensitive active ingredient selected from vitamins, amino-acids, nucleic acids, polypeptides and mixtures thereof, said hydrogel being adapted to control the release of said active ingredients in either humans or animals.

2. Preparations according to claim 1 in which said active ingredients are vitamins and are present preferably within 5-25 wt% of the total weight of the preparation.

3. Preparations according to claim 2 in which said vitamins are selected from vitamins A, B, C, D, E , K and mixtures thereof.

4. Preparations according to claim 3 in which said vitamin is vitamin A.

5. Preparations according to claim 3 in which said vitamin is vitamin C.

6. Preparations according to claim 1 in which said thermo- or photo sensitive active ingredients comprise liposoluble ingredients.

7. Preparations according to claim 1 in which said thermo– or photo-sensitive active ingredients comprise hydrosoluble ingredients.

8. Method of making the preparations of claim 6 comprising the following steps:

a) dissolving said liposoluble active ingredients in an appropriate solvent so as to form a solution;

b) adding the solution created in a), under agitation, to a xanthan solution so as to form a mixture;

c) spraying the mixture created in b) into a chitosan solution; and

d) recuperating of the hydrogel thus formed,

wherein steps a) to d) are essentially conducted in the absence of oxygen (air) and light.

9. Method of making the preparations of claim 7 comprising the following steps:

a) spraying a solution of xanthan into a solution of chitosan so as to form a hydrogel;

b) recovering the hydrogel formed in (a) followed by freeze-drying (or lyophilisating) the hydrogel;

c) introducing the freeze-dried hydrogel into an aqueous solution comprising at least one of said hydrosoluble active ingredients;

d) incorporating said hydrosoluble active ingredient(s) in the hydrogel by diffusion into the swollen hydrogel having a swelling index of 2000% or beyond to obtain a loaded hydrogel;

e) recovering said loaded hydrogel.

10. Method according to claim 9 wherein in said step c), said hydrosoluble active ingredient are stabilized by the addition of amino-acids.

11. Method according to claim 10 in which said amino-acids are chosen among L-cysteine, L-cystine and L-methionine and mixtures thereof.

12. Method according to claim 9 wherein in said step (c), said hydrosoluble active ingredient are stabilized by the addition of tripeptides.

13. A dermatological product comprising the preparations of claim 1.

14. The dermatological product of claim13, wherein the product is a cream.

15. The dermatological product of claim 14 wherein said thermo- and photosensitive substance is vitamin A.

16. A food additive comprising the preparations of claim 1.

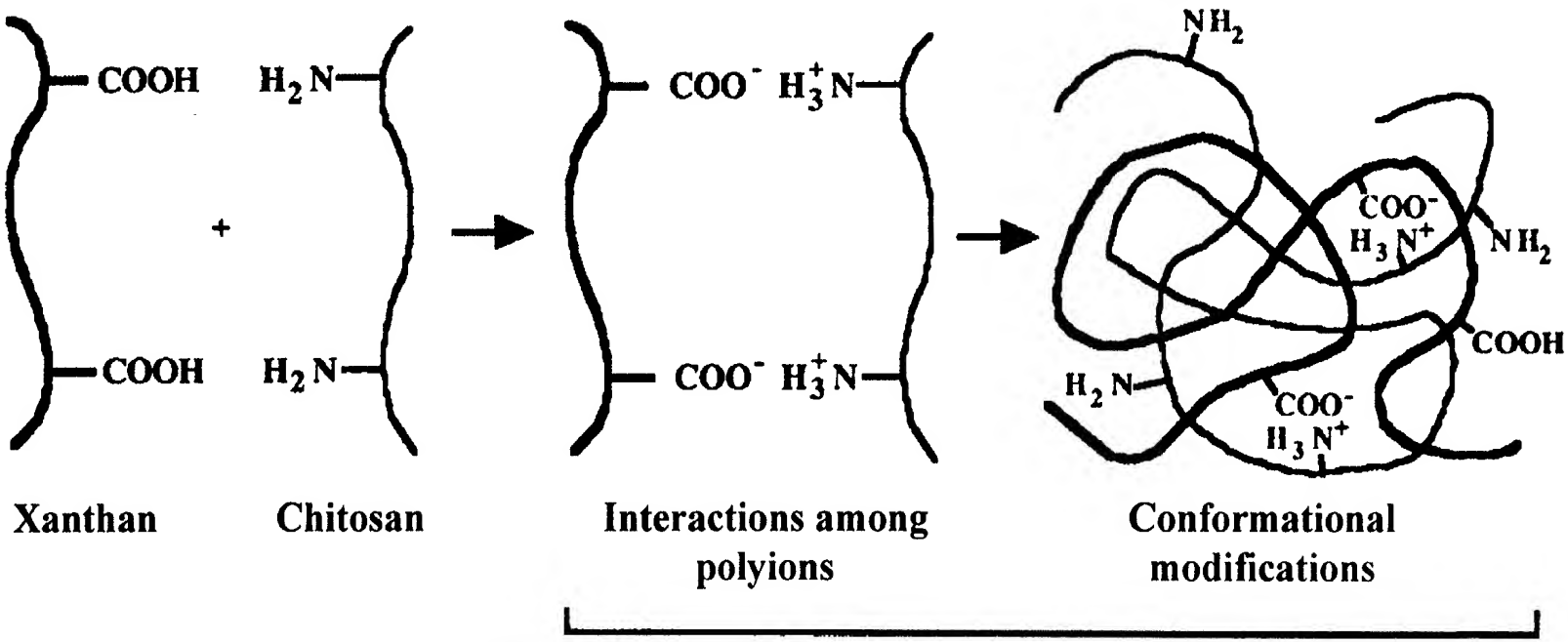

Figure 1

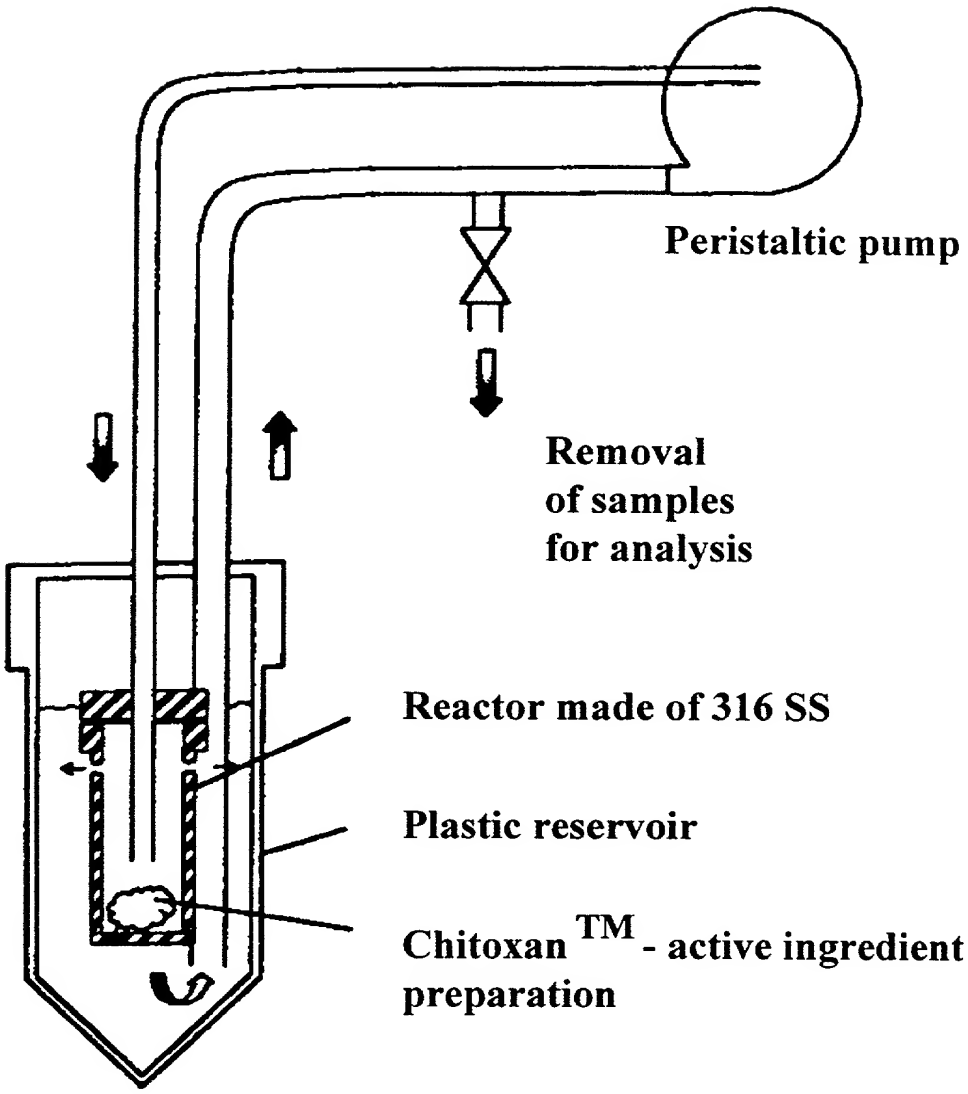

Figure 2

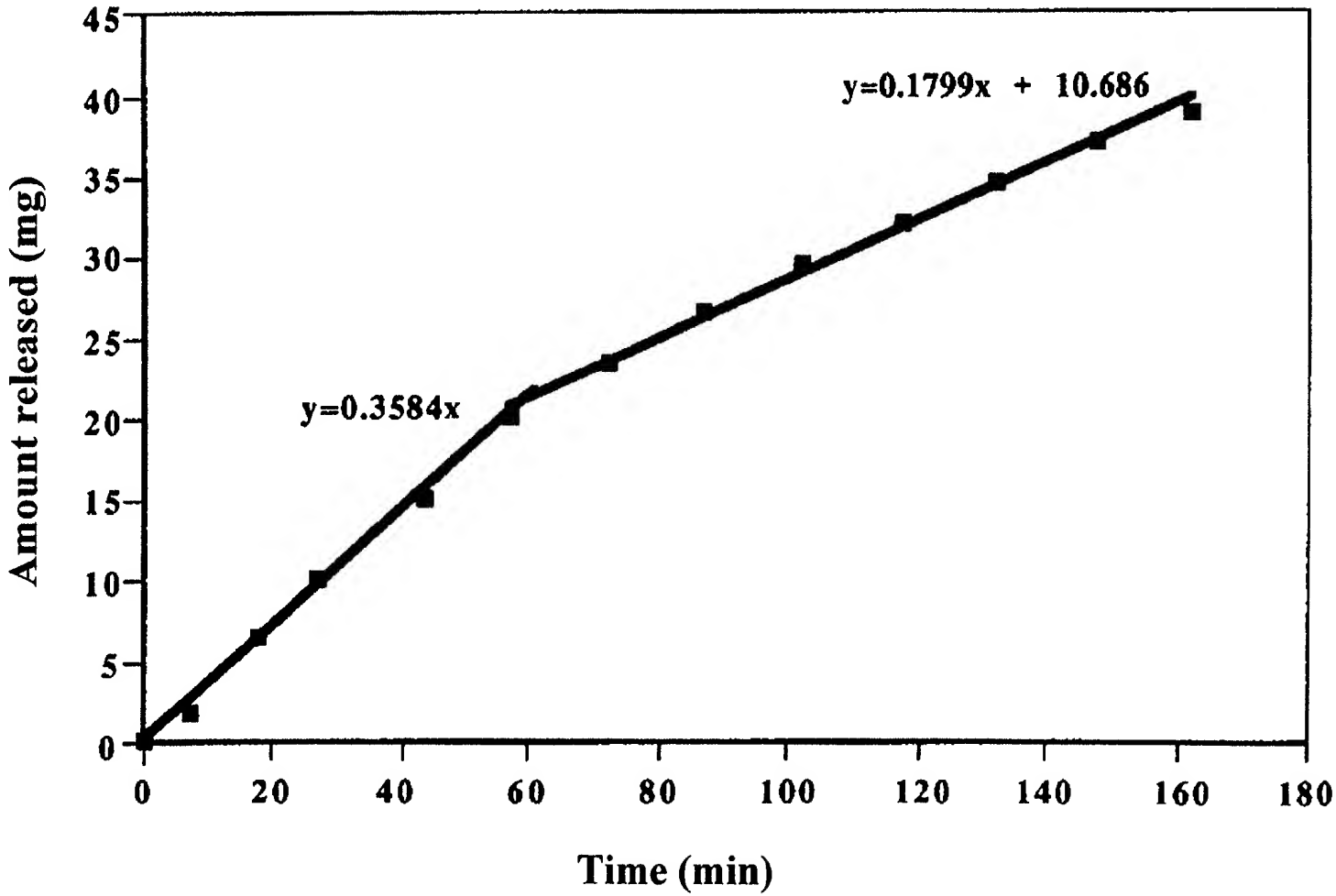

Figure 3

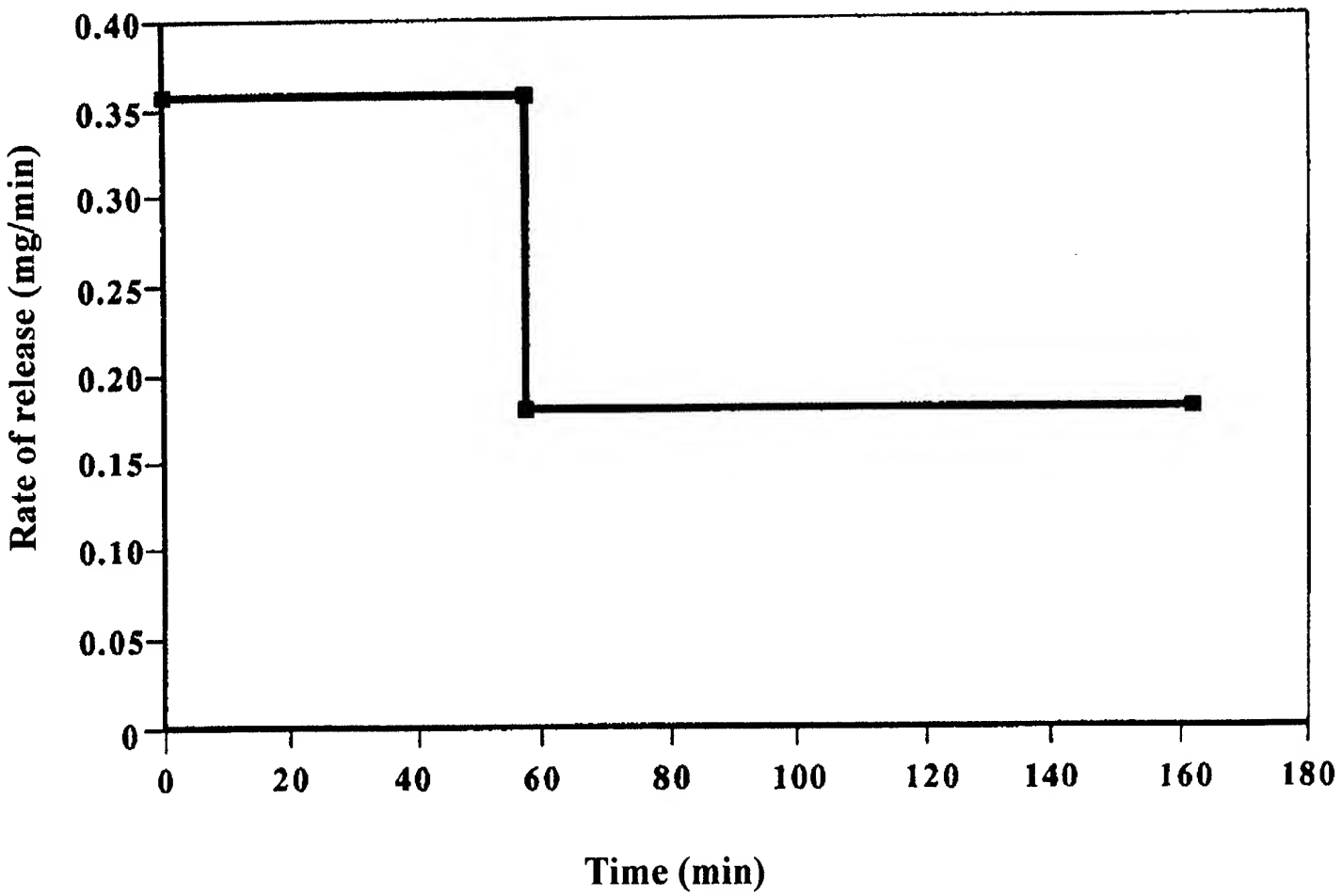

Figure 4

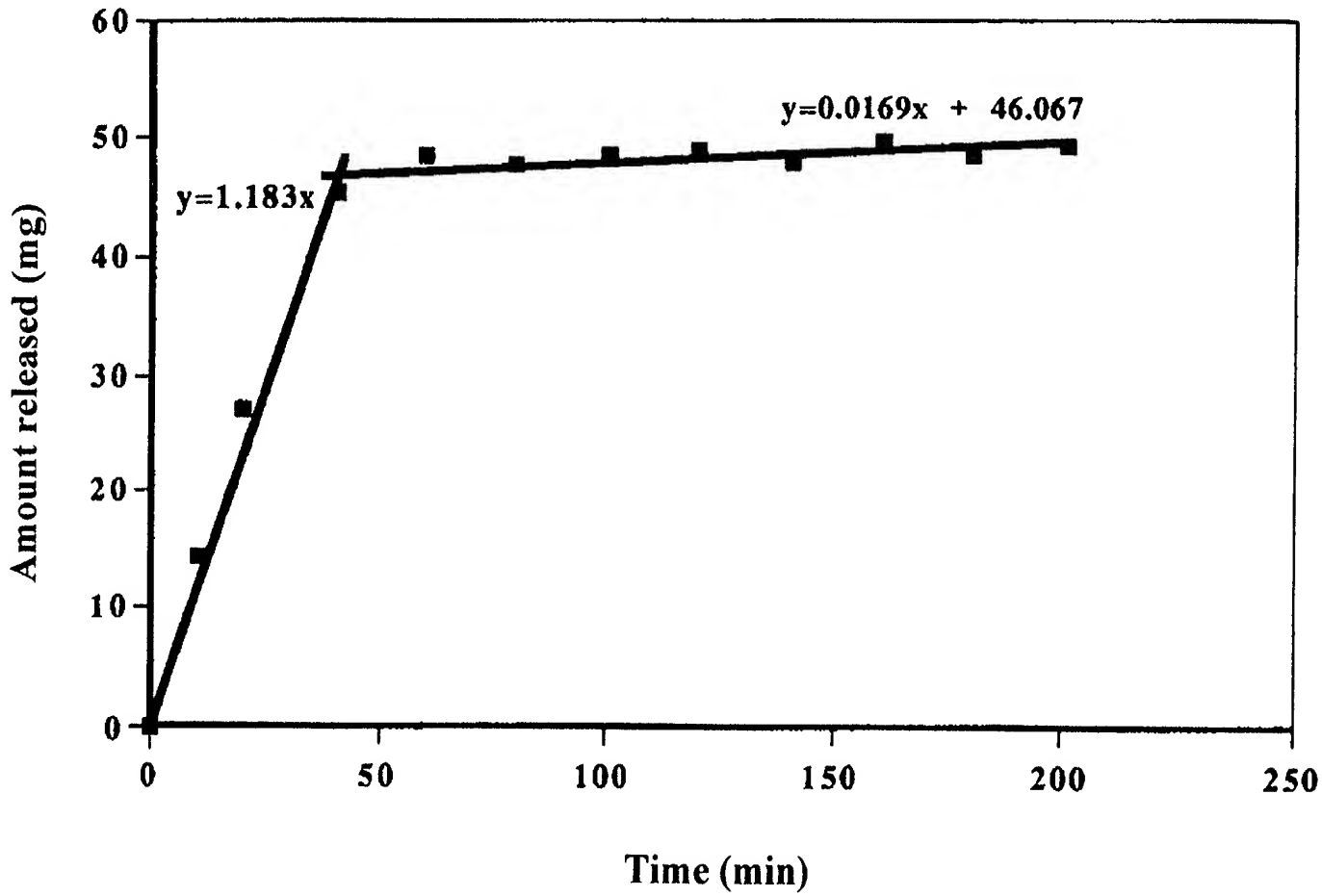

Figure 5

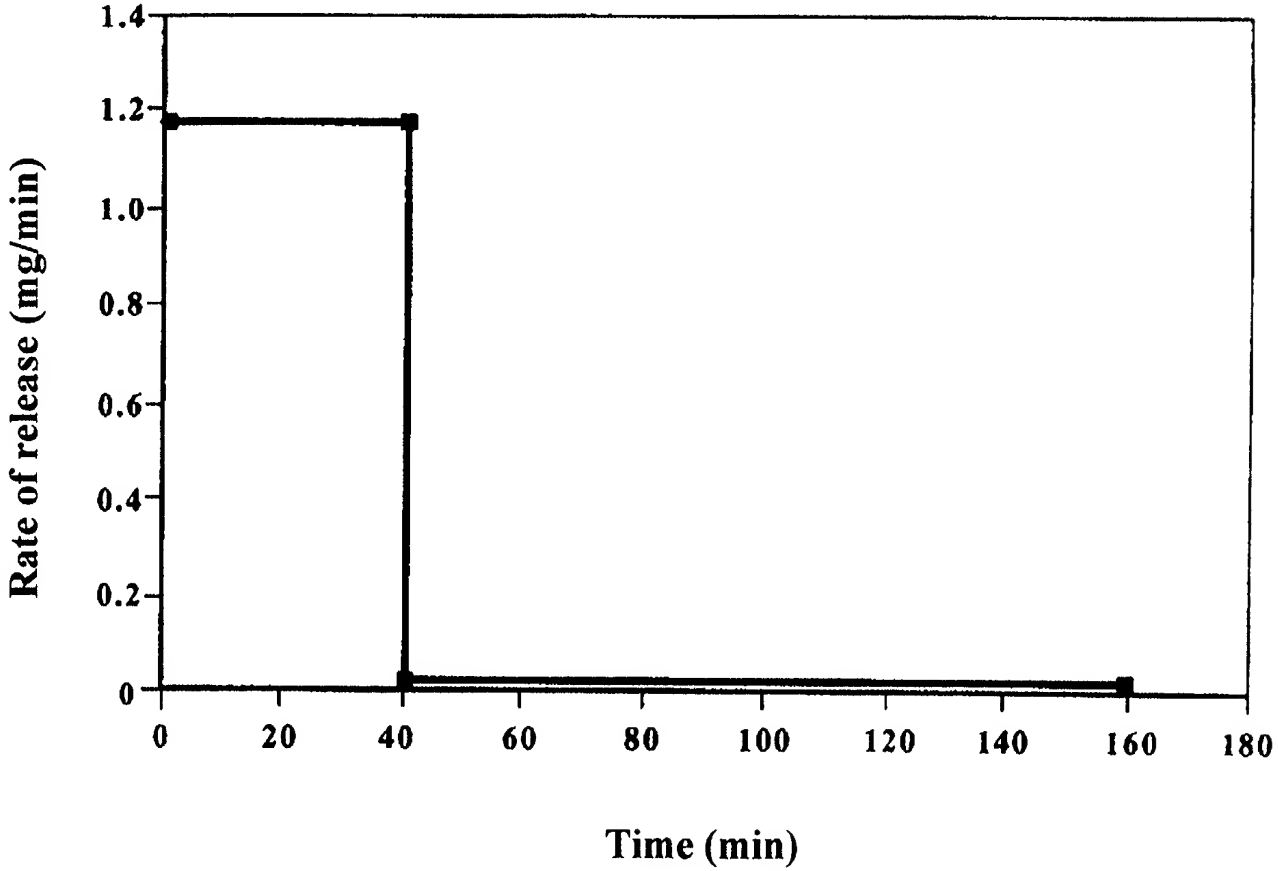

Figure 6

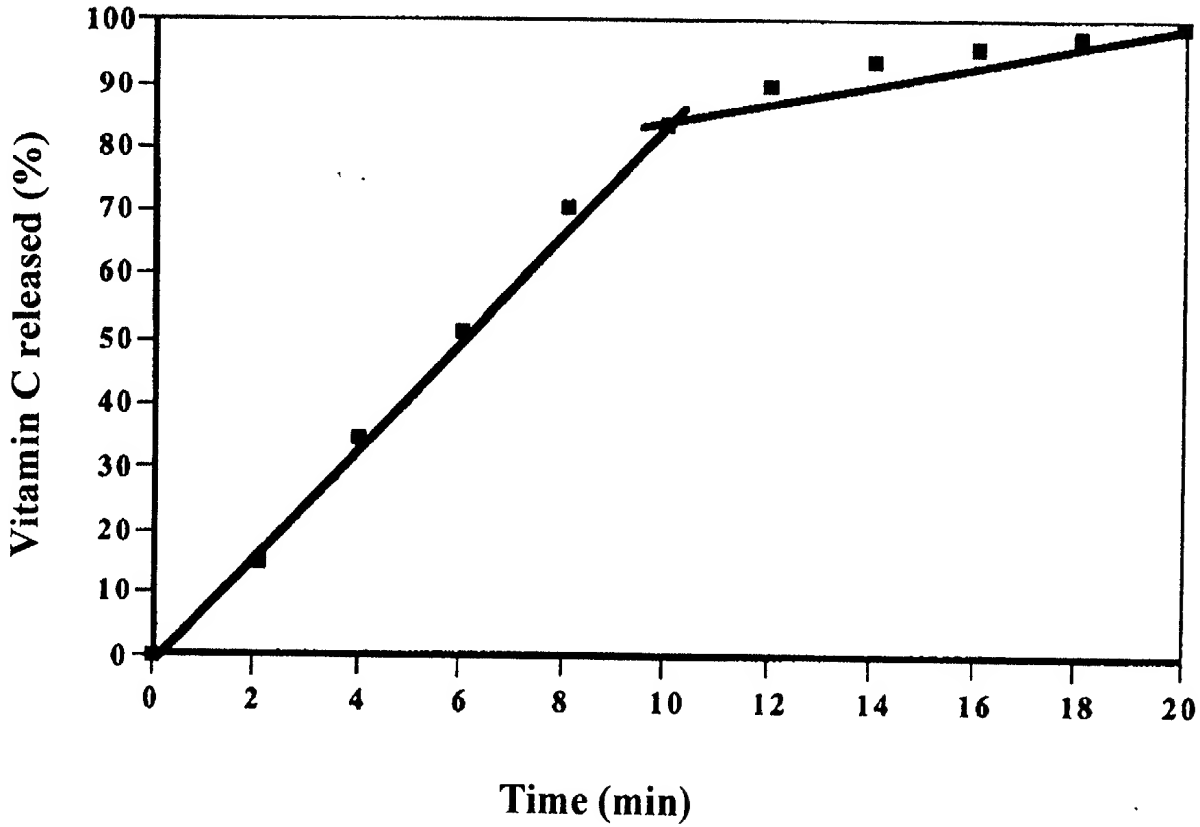

Figure 7

Docket No.
AML/10857.236

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

CHITOSAN-XANTHAN BASED POLYIONIC HYDROGELS FOR STABILISATION AND CONTROLLED RELEASE OF VITAMINS.

the specification of which

(check one)

☒ is attached hereto.

☐ was filed on _____ as United States Application No. or PCT International Application Number _____

and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed
2,243,619	CANADA	17/07/1998	☐
(Number)	(Country)	(Day/Month/Year Filed)	
			☐
(Number)	(Country)	(Day/Month/Year Filed)	
			☐
(Number)	(Country)	(Day/Month/Year Filed)	

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional application(s) listed below:

(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

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